Association between inflammatory biomarkers and neointimal response following elective implantation of the ABSORB bioresorbable vascular scaffold

Article (Accepted Version)

Full title **Association between inflammatory biomarkers and neointimal response following elective implantation of the ABSORB BVS**

Authors: Rajiv Rampat[1,2], Timothy Williams[1,2], Thomas Mayo[2], Manuela Mengozzi[2], Pietro Ghezzi[2], David Hildick-Smith[1], James Cockburn[1]

Address: [1]Sussex Cardiac Centre, Brighton and Sussex University Hospitals, UK, BN2 5BE. Tel +441273664571 Fax : +441273664580

[2]Brighton and Sussex Medical School, UK, BN1 9PX. Tel: +441273606755

Declaration I acknowledge that all the above authors meet the authorship criteria and that they are all in agreement with the manuscript

Correspondence: Rajiv Rampat, Sussex Cardiac Centre, Brighton and Sussex University Hospitals, UK, BN2 5BE. Tel +447739583320 rampat@doctors.org.uk

Key words: Bioresorbable vascular scaffold; inflammation; CRP; sCD40 ligand; MCP; IL-6

Word count 2674

Disclosures

This work was supported by an unrestricted grant from the Sussex Heart Charity (Registered in England and Wales - Charity number: 1120998). The funder did not play any part in the study. ABSORB scaffolds were provided free of charge by Abbott Vascular. The OFDI imaging catheters were provided free of charge by Terumo Inc. Neither companies had any role in the study beyond the provision of consumables outlined above.

ABSTRACT

Introduction

The ABSORB bioresorbable vascular scaffold (BVS) is associated with greater neointimal proliferation and thrombotic rate than metal stent. The role of inflammatory biomarkers on neointimal proliferation has not been studied in the setting of BVS implantation.

Methods

Thirty patients had arterial blood sampling before elective PCI with the ABSORB BVS and at 9 month follow up. Plasma levels of IL-6, soluble CD40 ligand (sCD40L), monocyte chemotactic protein-1 (MCP-1) and CRP were measured using ELISA. Baseline and follow up levels were compared for each biomarker. Optical frequency domain imaging (OFDI) was performed at follow up and the neointimal burden was calculated as the ratio of neointimal area to scaffold area. The levels of inflammatory mediators were correlated with neointimal burden.

Results

There was no significant increase in the levels of biomarkers from baseline to follow up. Median CRP levels changed from 1.1 [Interquartile range (IQR): 0.5-2.5] to 2.2 (IQR: 0.5-3.5) μg/ml, IL-6 from 1.0 (IQR: 0.6-1.4) to 1.0 (95% CI: 0.6-1.4) pg/ml, MCP-1 from 120.4 (IQR: 86.0-153.4) to 102.0 (IQR: 70.3-148.1) pg/ml and sCD40L from 108.3 (IQR: 74.1-173.7) to 112.0 (IQR: 71.0-225.9) pg/ml. The average neointimal burden in the cohort was 18% (±6). Baseline, follow up and change in

plasma levels of inflammatory markers between these two time points did not correlate with neointimal burden.

Conclusion

Elective PCI with the ABSORB BVS does not provoke a chronic inflammatory response. The degree of neointimal proliferation after elective implantation of the ABSORB BVS is independent of the pre-exisiting inflammatory environment.

CONDENSED ABSTRACT

Elective PCI with the ABSORB BVS does not increase plasma levels of inflammatory biomarkers and therefore does not appear to cause persistent inflammation at medium term

The neointimal response after elective implantation of the ABSORB BVS is independent of the baseline inflammatory environment.

Thrombotic predisposition at baseline may play a role in the development of subsequent scaffold thrombosis.

MANUSCRIPT

Introduction

Randomised controlled trials and registry data have shown that the ABSORB bioresorbable vascular scaffold (BVS) is associated with a higher rate of thrombosis and late luminal loss(1, 2). Some of the contributory factors such as malapposition, late scaffold dismantling and underdeployment(3) have been identified but the influence of inflammation on the restenotic/thrombotic response has not been investigated. It is known that metal stents can induce chronic inflammation causing a potent neointimal response and a high rate of in-stent restenosis (ISR)(4). Histopathological analyses of restenotic tissue have shown a higher preponderance of inflammatory cells and fibrinoid tissue indicating an incomplete healing response(5). Biological factors responsible for this phenomenon include hypersensitivity reactions either to the metallic platform or to the polymer jacket and resistance to the anti-proliferative drug(6, 7). In contrast, healthy porcine coronary arteries treated with the ABSORB BVS have shown a relatively benign vessel response compared to first generation drug eluting stents(8). Whether the lower levels of inflammation seen in these pre-clinical studies can be extrapolated to diseased human arteries is unknown.

The inflammatory response after PCI is influenced not only by the vascular injury induced by the procedure but also by the pre-existing inflammatory environment. In clinical settings, the baseline inflammatory status has been assessed with a wide variety of markers including CRP, IL-6, MCP-1 and sCD40L. Patients with high pre-interventional inflammatory activation seem to be at a greater risk of ISR(9-13). So far no study has investigated the effect of pre-procedural inflammatory state on subsequent neointimal growth after treatment with BVS.

Methods

Study design and population

The study population consisted of 30 patients who had elective PCI with the ABSORB BVS for bifurcation disease. The inclusion criteria was the presence of 'false' bifurcation disease (Medina type 1,1,0 or 1,0,0 or 0,1,0) with >70% stenosis in the main vessel and a side branch diameter >2mm on visual assessment. Major exclusion criteria were acute presentation either with unstable angina or acute coronary syndrome, bifurcation disease involving the left main stem and chronic total occlusion of either the main vessel or side branch. All patients were recruited from a single centre between February 2015 and July 2016. As part of the research protocol, all patients had peripheral arterial blood sampling before PCI (baseline) and 9 months after the procedure (follow up). Informed consent was obtained from all participants. Patients underwent optical frequency domain imaging (OFDI) post BVS implantation and at follow up. The clinical investigational plan, consent form and all amendments to these study documents were reviewed and approved by the South East Coast (Brighton and Sussex) Research Ethics Committee.

Biochemical analysis

Two sets of 10 ml blood samples were taken from the arterial sheath from each patient, first before scaffold implantation and again at 9 months after implantation. Blood was collected in EDTA-tubes (BD Vacutainers, purple cap) and centrifuged at 1,500 rpm for 10 min. The resulting plasma was collected and aliquoted into 5 samples of 500 µl each. All samples were processed and frozen within 3 hours of collection. Samples were stored at -80˚C at the local hospital. These were transferred on dry ice to the laboratory for analysis. Plasma levels of inflammatory markers were

measured by enzyme-linked immunosorbent assay (ELISA) using commercially available assay kits from DRG Diagnostics, Marburg, Germany (high-sensitivity CRP) and Bio-Techne, Minneapolis, USA (high-sensitivity IL-6, sCD40L and MCP-1).

OFDI acquisition and analysis

OFDI imaging was performed using the FastView catheter R and the Lunawave coronary imaging console (Terumo Corporation, Tokyo, Japan). The OFDI catheter was carefully advanced over a guidewire beyond the target area. While contrast was continuously injected at a rate of 4ml/s, OFDI images of the main vessel were acquired at a rate of 160 frames/second with a pullback speed of 20mm/s.

OFDI analysis was performed offline using software provided by Terumo (Terumo Corporation, Toyko, Japan). Quantitative measurements were performed at 1mm intervals starting from the first image where at the scaffold was visible in at least 3 quadrants. In each slice, the abluminal scaffold area, total strut area and luminal area were measured. Neointimal burden was calculated as the percentage of neointimal area to scaffold area as shown below(14).

$$Neointimal\ burden\ =\ (Neointimal\ area/\ Scaffold\ area\ )x100\ \%$$

Statistical analysis

Continuous variables are presented as mean (± standard deviation) if normally distributed and median (interquartile range [IQR]) when not normally distributed. Discrete data is presented as percentage (count). Test for normality was performed with the Shapiro-Wilk test. The distribution of inflammatory biomarker levels was non-normal and thus comparison between baseline and follow up levels were made

using the Wilcoxon signed rank test. Correlation between levels of inflammatory markers and neointimal burden was made using the Spearman rank correlation coefficient. The level of statistical significance for hypothesis testing was $p<0.05$. All statistical calculations were performed using SPSS software (version 24, SPSS Inc., Chicago, Illinois).

Results

Population characteristics

Table 1 summarises the patient and procedural characteristics at baseline. Twenty three patients (77%) were male and mean age was 62.8 years. All patients had stable coronary disease. None of the patients had a pre-existing inflammatory condition, renal or liver dysfunction. Procedural success was 100%. Mean follow up period was 313 (± 50) days.

Imaging results at 9 months

There were no cases of either binary restenosis or thrombosis. All stented vessels and side branches were widely patent. Vascular response was fairly benign with an average neointimal burden of 18 (± 6) %. Mean in-scaffold luminal diameter reduced from 2.89 (± 0.35) mm to 2.70 (± 0.39)mm ($p=0.0001$).

Relationship between baseline and follow up levels of inflammatory markers

Table 2 compares the baseline and follow up levels of each marker. None of the inflammatory markers showed a significant change in plasma level from baseline to follow up.

Relationship between inflammatory markers and neointimal growth

Table 3 summarises the Spearman correlation between each marker and neointimal burden on follow up OFDI. We investigated levels at baseline, follow up as well as the difference in levels between the two time points (Δ= follow up levels – baseline levels). None of these parameters showed a significant association with the degree of neointimal growth at 9 months. It is worth mentioning one case where the patient had a significantly elevated sCD40L baseline level of 2421 pg/ml compared to the cohort median of 108 pg/ml. The patient's clinical and procedural characteristics were not significantly different from those in the group. Interestingly, there was a large amount of intracoronary thrombus evident on OFDI shortly after BVS deployment despite pre-procedural treatment with DAPT (Figure 1). By 9 months, the sCD40L level had reduced to 71 pg/ml. OFDI imaging at that time point did not demonstrate persistent thrombus or an excessive hyperplastic response (neointimal burden 19%)

Discussion

Our study is the first to look at the influence of serum markers of inflammation in the context of PCI with the ABSORB BVS. The findings of our study can be summarised as such: 1) BVS implantation in an elective setting does not cause persistent inflammation at 9 months as assessed by serum inflammatory markers; and 2) the extent of neointimal tissue growth is independent of the inflammatory status at baseline and follow up.

BVS implantation in an elective setting is not associated with persistent inflammation at 9 months

Elective stenting initiates a complex cascade of physiological processes aimed at repairing the vessel. This local inflammatory process can be assessed using indices in the peripheral blood (15, 16). Persistence of the inflammatory process after stent implantation changes the physiological reparative response to a pathological one. The underlying inflammatory environment is a strong predictor of in-stent restenosis and stent thrombosis (17). In the clinical setting, this chronic inflammatory response causes elevated levels of systemic biomarkers, which can be used as a surrogate marker for the underlying inflammatory status (18).

Based on our study, the polymer and its degradation products do not seem to evoke a systemic inflammatory response at medium term after the ABSORB BVS is implanted in an elective setting. Despite extensive published literature on the ABSORB BVS, the inflammatory response in humans is still poorly understood. Chronic low grade inflammation induced by either the polymer or its degradation products has been postulated as one possible cause for the high thrombotic rate(3). However both PLLA(19) and PDLLA(20) polymers have been used in the human coronary artery without major safety concerns. The final degradation products of the scaffold are D-lactic acid and L-lactic acid both of which naturally occur in the body. The amount of these products dispersed into the body as a result of scaffold disintegration is far below the normal reference levels in the body (21). It does not appear that the intermediate oligomers elicit a toxic tissue response either, at least in animal studies. In a swine model implanted with BVS, the percentage of struts with giant cells and granulomas decreases progressively over 24 months(8) and in a swine model PDLLA-based BRS induce inflammation with a peak at 6 months and decreasing thereafter(22).

However inflammation may play a more prominent role in the more advanced stages of bioresorption. While the vascular response in porcine arteries is relatively benign, the inflammation score is at its peak between 12 and 18mths(23). This timing coincides with the highest rate of mass loss and formation of degradation products.

Our findings are supported by the comparable incidence of binary restenosis at 1 year between BVS and Xience DES seen in ABSORB China(24) and Japan(25).

The extent of neointimal tissue growth at 9 months is independent of the inflammatory status at baseline and follow up

The biologic response to the ABSORB BVS is probably closer to that following PCI with DES than with BMS. While the predictive role of preprocedural inflammation in the development of BMS restenosis is well established, its significance in patients receiving DES is less clear. Several studies have failed to demonstrate an association between neointimal hyperplasia and either pre or post interventional biomarker levels in DES restenosis(10, 26, 27). The release of potent antiproliferative agents in DES alters the biological response to vessel injury. Limus analogues have anti-inflammatory properties in addition to their inhibitory effect on the cell cycle. In particular, everolimus has been found to inhibit neutrophil activation, mitigate pro-inflammatory TNF related pathways and promote the release on the anti-inflammatory cytokines(28, 29). In addition, inhibition of the mTOR pathway in platelets prevents platelet activation and aggregation. This suppressive effect on inflammation may explain the lack of correlation we observed between baseline inflammatory status and neointimal growth.

We also did not observe any association between follow up levels of inflammatory markers and intensity of neointimal response. It is possible that the excessive hyperplastic response seen in restenosis is effected through mechanisms other than inflammation. In contrast to restenosis in BMS, a heterogeneous tissue composition is observed in most cases of BVS restenosis. In particular, restenotic lesions that occur more than 6 month after implantation show signs suggestive of neoatherosclerosis(30). Such systemic processes may play a more important role than locally induced inflammation in the pathology of BVS restenosis.

Finally, the case of very high pre-procedural sCD40L level deserves special mention. sCD40L not only plays a role in inflammation but also in platelet activation after plaque rupture, as the CD40/CD40L complex increases the expression of tissue factor while thrombomodulin expression is reduced thus creating a procoagulant state(31). Studies using IL-6 and other markers as surrogates of inflammation have compared levels of sCD40L in both healthy subjects and cardiac patients(32). sCD40L levels appears to be more a marker of platelet activation than inflammation in patients with coronary artery disease. The large thrombotic burden evident on OFDI in conjunction with the very high pre-procedural sCD40L suggest that pre-existing thrombotic propensity may be an important factor in the development of scaffold thrombosis. The identification of such individuals may be key to the challenging issue of in-scaffold thrombosis. The choice of appropriate biomarkers of platelet activation for risk stratification warrants further investigation.

Limitations

The main limitation of our study is its small sample size. This was a single centre study and our data may not be applicable to all patients. Baseline inflammatory marker levels were low in our group and our results may not be applicable in the higher inflammatory environment of acute coronary syndromes. None of the patients in our cohort had extensive neointimal proliferation on OFDI or angiographic in-stent restenosis. It is possible that inflammatory markers only show discriminatory power in patients with large neointimal burden. Furthermore, our study design was limited to 9 months with an OFDI endpoint. Thus we cannot comment on the role of inflammation in the advanced stages of the resorption process. Very late ISR and thrombosis may progress through different pathological mechanisms that would not have been identified in our study.

Conclusions

Elective implantation of the ABSORB BVS does not elicit persistent inflammation within the coronary artery at medium term. The neointimal response after scaffold implantation is independent of the underlying inflammatory environment before scaffold implantation and at follow up. Thrombotic predisposition at baseline may play a part in the development of subsequent scaffold thrombosis. Future studies are needed to investigate this observation.

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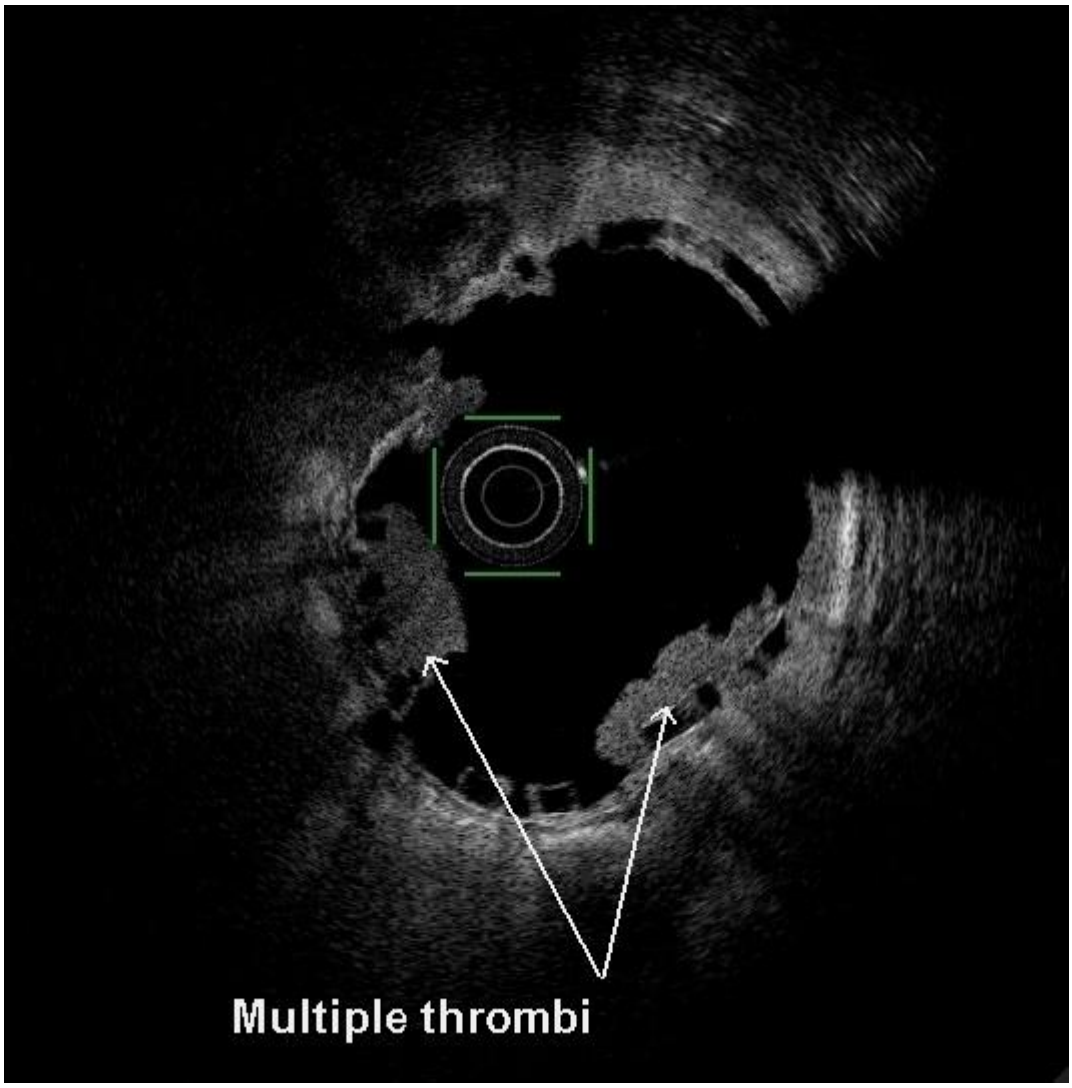
LIST OF FIGURES

LIST OF FIGURES

Figure 1: OFDI image demonstrating multiple thrombi after BVS deployment. The patient had a significantly elevated baseline level of sCD40L (2421 pg/ml) compared to the cohort median (108 pg/ml).



LIST OF TABLES

Table 1: Clinical and procedural characteristics of study cohort

Patient characteristics	
Age	62.8 (± 10.4)
Gender (male)	76.7 (23)
BMI	28.3 (± 5.1)
Hypertension	46.7 (14)
Hyperlipidaemia	14 (46.7)
Current smoker	5 (16.7)
Diabetes Mellitus	5 (16.7)
Family History of IHD	11 (36.7)
Creatinine (μmol/l)	84.7(± 15.3)
Previous MI	33.3 (10)
Previous PCI	36.7 (11)
Previous CABG	0
Previous Stroke/TIA	3.3 (1)
PVD	0
Inflammatory condition	0
Stable angina	20 (66.7)
Silent ischaemia	10 (33.3)
ACS	0
Lesion characteristics	
B2/C lesion	20 (66.7)
Mod/severe calcification	10 (33.3)
Procedural characteristics	
BVS Diameter (mm)	3.0 (± 0.3)
BVS Length (mm)	23.9 (± 6.9)
Number of BVS	1.1 (± 0.3)
Procedural success	100 (30)

Data expressed as frequency (no of patients) or mean (± sd)

Table 2: Inflammatory marker levels were measured at baseline (before scaffold implantation) and at follow-up (9 months after scaffold implantation) in 30 patients, and the median and interquartile range is reported. The changes between baseline and follow-up inflammatory markers levels were analysed by Wilcoxon signed-rank test and the p value is reported.

	Baseline	**Follow-up**	**p value**
CRP (μg/ml)			
median (IQ range)	1.1 (0.5-2.5)	2.2 (0.5-3.5)	0.082
IL-6 (pg/ml)			
median (IQ range)	1.0 (0.6-1.4)	1.0 (0.60-1.4)	0.975
MCP-1 (pg/ml)			
median (IQ range)	120.4 (86.0-153.4)	102.0 (70.3-148.1)	0.061
sCD40L (pg/ml)			
median (IQ range)	108.3 (74.1-173.7)	112.0 (71.0-225.9)	0.734

Table 3: Correlation between levels of inflammatory markers (baseline, follow up and the difference between the two denoted as Δ) and neointimal burden quantified on OFDI was made using the Spearman rank correlation coefficient.

Marker	Spearman Correlation coefficient	p value
CRP baseline	0.03	0.89
CRP fup	-0.05	0.81
ΔCRP	-0.11	0.57
IL-6 baseline	0.22	0.25
IL-6 fup	0.25	0.18
ΔIL-6	0.06	0.74
MCP-1 baseline	-0.16	0.4
MCP-1 fup	0.05	0.8
ΔMCP-1	0.2	0.28
sCD40L baseline	-0.13	0.51
sCD40L fup	0.18	0.35
ΔsCD40L	0.22	0.25